

# Overview of Thiophanate-methyl Risk Assessment

July 25, 2001

## *Introduction*

This document summarizes EPA's human health and ecological risk findings and conclusions for the fungicide thiophanate-methyl, as presented fully in the documents, "Thiophanate Methyl: HED Revised Preliminary Risk Assessment" dated June 25, 2001, and "EFED's RED Document for Thiophanate-methyl and its Major Degradate, MBC" dated May 9, 2001. The purpose of this summary is to assist the reader by presenting the key features and findings of these risk assessments, and to enhance understanding of the conclusions reached in the assessments. This overview was developed in response to comments and requests from the public which indicated that risk assessments were difficult to understand, that they were too lengthy, and that it was not easy to compare the assessments for different chemicals due to the use of different formats.

The risk assessments noted above as well as the supporting documents, are available on EPA's Internet site ([www.epa.gov/pesticides/reregistration/thiophanate-methyl.htm](http://www.epa.gov/pesticides/reregistration/thiophanate-methyl.htm)) and in the Pesticide Docket for public viewing. Meetings with stakeholders (i.e., growers, extension personnel, commodity groups, and other government officials) are planned to discuss the identified risks and to solicit input on risk mitigation strategies. This feedback will be used to complete the Reregistration Eligibility Decision (RED) document, which will include the resultant risk management decisions. The Agency plans to conduct a closure conference call with interested stakeholders to discuss the regulatory decisions presented in the RED.

The Food Quality Protection Act (FQPA) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity." Although it is possible that thiophanate-methyl or its primary metabolite, carbendazim (MBC), may express toxicity through a common mechanism with other compounds, at this time, the Agency does not have sufficient reliable information to make this determination. Consequently, the risks summarized in this document are only for thiophanate-methyl and MBC. If EPA identifies other substances that share a common mechanism of toxicity with thiophanate-methyl or MBC, aggregate exposure assessments will be performed on each chemical, followed by a cumulative risk assessment.

EPA, however, did evaluate the aggregate exposures to MBC resulting from registered uses of thiophanate-methyl and MBC. MBC is not only the primary metabolite of thiophanate-methyl, it is

also a registered fungicide for use in tree injection<sup>1</sup> and as a fungicide/preservative in paints, coatings, plaster and adhesives (which may be used in residential settings). Note that MBC is also a primary metabolite of benomyl; however, exposure to benomyl-derived MBC was not considered in the risk assessment because the technical registrant for benomyl, DuPont, has requested voluntary cancellation of all of its products containing benomyl. If any other registrant supports continued or new benomyl uses, EPA will evaluate the additional risk posed as a result of those uses.

## **Use Profile**

- **Fungicide:** Thiophanate-methyl is a systemic fungicide of the benzimidazole class registered for use on the following food/feed crops: almonds, apples, apricots, dry beans, green beans, cantaloupes, cherries, cucumbers, melons, nectarines, onions, peaches, peanuts, pecans, plums, potatoes, pumpkins, soybeans, squash, strawberries, sugar beets, watermelons, and wheat. A tolerance has been established with no U.S. registration to permit importation of thiophanate-methyl-treated bananas. Non-food/feed uses include ornamentals (greenhouses, interiorscapes, landscaping, and nursery) and turf (sod farms, residential and recreational lawns).
- **Formulations:** Thiophanate-methyl formulations include dust, granular, wettable powder, water-dispersible granular, and flowable concentrate, ranging from 1.5% to 90% active ingredient. Common trade names: Topsin<sup>®</sup>, Banrot<sup>®</sup>, Systec<sup>®</sup>, Fungo<sup>®</sup>, Duosan<sup>®</sup>.
- **Methods of Application:** May be applied using aerial, ground, chemigation, or hand-held equipment. The majority of crops are treated with postemergent broadcast applications.
- **Use Rates:** Single application rates vary widely depending on the crop/pest, as follows:  
  
*Orchard crops:* 0.35-1.6 lb ai/acre; *field crops (except onions):* 0.2-1.4 lb ai/acre; *onions:* 11-15 lb ai/acre; *peanut/potato seed pieces:* 0.25 lb ai/100 lb. of seed; *greenhouse bulbs:* 0.34 lb ai/100 gal dip; *horticultural/greenhouse:* 0.5 lb ai/100 gal, 0.03-0.87 lb ai/1000 ft<sup>2</sup>; *turf:* #19 lb ai/acre ( typically 11-15 lb ai/acre).
- **Annual Poundage:** Total annual domestic usage of thiophanate-methyl is approximately 450,000 lbs a.i. for about 750,000 acres treated (excluding use on onions, potatoes, turf, and ornamentals for which EPA has no usage data). Largest markets in terms of total pounds active ingredient include soy beans (110,000 lbs a.i.), sugar beets (75,000 lbs a.i.), and wheat (51,000 lbs a.i.). Crops with over 20 percent of acres treated include: peaches (26%) and strawberries (21%). Use has increased considerably in recent years and is expected to

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<sup>1</sup>Tree injection products are restricted to ornamental trees only; labels specify product is not to be used on trees which will produce food within the year following treatment.

continue rising significantly due to the cancellation of benomyl-containing products.

- **Classification:** General use pesticide.
- **Technical Registrant:** Cerexagri, Inc. (previously known as Elf-Atochem North America, Inc.)

## **Hazard**

Thiophanate-methyl and carbendazim (MBC) are of low toxicity following acute oral, dermal and inhalation exposures (toxicity categories III/IV). Thiophanate-methyl is classified as a skin sensitizer, while MBC is not a skin sensitizer. Thiophanate-methyl and MBC share some common toxicological effects, including developmental and liver effects. In all animal species, the most sensitive toxicological effect is liver toxicity following subchronic and chronic oral exposure to both thiophanate-methyl and MBC. The thyroid gland is also one of the most sensitive target organs for thiophanate-methyl following oral exposures.

Both thiophanate-methyl and MBC induce developmental toxicity. Fetal effects from thiophanate-methyl exposure include an increase in supernumerary ribs and reduced fetal weight. The developmental effects of MBC occurred in the absence of maternal toxicity, indicating increased fetal susceptibility. In rats, adverse fetal effects attributed to maternal MBC exposure include decreased body weight, increases in skeletal variations and malformations, and ocular and brain malformations. MBC is also associated with adverse reproductive effects, including testicular effects such as reduced sperm counts, reduced testes size, and testicular pathology.

Both thiophanate-methyl and MBC have been associated with an increased incidence of mouse liver tumors following chronic oral exposure. MBC has weak mutagenic activity that is primarily attributed to adverse effects on cellular spindle apparatus. In addition, both thiophanate-methyl and MBC cause aneuploidy (i.e., abnormal number of chromosomes).

## **Human Health Risk Assessment**

Risks from dietary exposure (food and drinking water), residential exposure, aggregate exposures, and occupational exposures have been evaluated for thiophanate-methyl. Risks from exposure to MBC have also been evaluated since thiophanate-methyl rapidly degrades to MBC in the environment. Therefore, MBC residues are present in food, drinking water, on lawns, etc., following thiophanate-methyl use.

Many of the human health assessments were performed separately for thiophanate-methyl and for the sum of the metabolites due to the use of different toxicological endpoints as well as to permit an

aggregate assessment of MBC exposures and risks resulting from the uses of both registered active ingredients (i.e. thiophanate-methyl and MBC). However, risk estimates from thiophanate-methyl and MBC are summed in those instances where thiophanate-methyl and MBC share common toxicological effects (i.e., developmental and liver effects and liver tumors) using a toxic equivalency factor (TEF) approach. The TEF approach essentially converts thiophanate-methyl exposure estimates into MBC equivalents to account for the differences in toxicity endpoints between thiophanate-methyl and MBC.

The following tables summarize the toxicological endpoints and doses that were used to complete the human health risk assessments for thiophanate-methyl and MBC:

**Table 1. Summary of Doses and Toxicological Endpoints for Thiophanate-methyl**

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females 13-50 yrs	NOAEL=20 mg/kg/day** UF = 100 <b>Acute RfD</b> = 0.2 mg/kg/day	FQPA SF = 3 <b>aPAD</b> = <u>acute RfD</u> FQPA SF = 0.067 mg/kg/day	1997 Rabbit Developmental Study LOAEL=40 mg/kg/day based on increases in the mean number of ossification sites in the thoracic vertebrae and ribs-pairs as well as a decrease in lumbar vertebrae at 40 mg/kg/day in fetuses of exposed dams. These conditions are collectively referred to as an increase in “supernumerary ribs”
Acute Dietary, General Population	NOAEL=40 mg/kg/day UF = 100 <b>Acute RfD</b> = 0.4 mg/kg/day	FQPA SF = 3 <b>aPAD</b> = <u>acute RfD</u> FQPA SF = 0.13 mg/kg/day	Chronic oral toxicity dog study LOAEL= 200 mg/kg/day based on tremors 2-4 hours post-dosing in 7 of 8 dogs.
Chronic Dietary	NOAEL=8 mg/kg/day UF = 100 <b>Chronic RfD</b> = 0.08 mg/kg/day	FQPA SF = 3 <b>cPAD</b> = <u>chronic RfD</u> FQPA SF = 0.027 mg/kg/day	Chronic oral toxicity dog study LOAEL= 40 mg/kg/day based on thyroid effects and decreased body weight.
Short-and Intermediate Term Incidental Ingestion	Oral NOAEL =10 mg/kg/day	<b>LOC for MOE = 300</b> for all residential populations	1997 Rabbit Developmental Study LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Short- and Intermediate-Term Dermal	Dermal NOAEL = 100	<b>LOC for MOE = 300</b> for all residential populations <b>LOC for MOE = 100</b> for occupational workers	21-Day Rabbit Dermal Toxicity Study LOAEL = 300 mg/kg/day based on decreased body weight (28%) and food consumption (15%).

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Short-and Intermediate Term Inhalation (a)	Oral NOAEL =10 mg/kg/day (inhalation absorption rate=100% relative to oral absorption)	<b>LOC for MOE = 300</b> for all residential populations <b>LOC for MOE = 100</b> for occupational workers	1997 Rabbit Developmental Study LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Cancer (a)	$Q1^* = 1.38 \times 10^{-2}$ (mg/kg/day) <sup>1</sup> (dermal absorption rate =7% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	$Q1^* = 1.38 \times 10^{-2}$ (mg/kg/day) <sup>1</sup>	78-week mouse study based on male mouse liver adenoma and/or carcinoma and/or hepatoblastoma combined tumor rates

\* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.

\*\* The acute dietary (Females 13+) NOAEL is different from the short- and intermediate-term incidental ingestion and inhalation NOAELs even though they are all based on the 1997 rabbit developmental study because the endpoint for Females 13+ (NOAEL = 20 mg/kg/day) was selected to account for *developmental* effects that can occur after a single oral dose. The NOAEL is 10 mg/kg/day for the other risk assessments because the endpoint is based on *maternal* effects (decreased body weight and food consumption) that occur after repeated oral exposures.

UF = Uncertainty Factor

PAD = Population Adjusted Dose (includes UF and FQPA safety factor)

LOC= Level of Concern

MOE = Margin of Exposure

(a) Since an oral value was selected, a 7% dermal absorption factor and 100% inhalation absorption factor (equivalent to oral absorption) were used for route-to-route extrapolation. The dermal absorption factor is based on the results of an oral developmental toxicity study and a 21-day dermal toxicity study in the same species (rabbit) with similar endpoints.

**Table 2. Summary of Doses and Toxicological Endpoints for MBC**

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute Dietary, Females 13-50 years	NOAEL=10 mg/kg/day UF = 100 <b>Acute RfD</b> = 0.1 mg/kg/day	FQPA SF = 10 <b>aPAD</b> = <u>acute RfD</u> FQPA SF = 0.01 mg/kg/day	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Acute Dietary, General Population, including infants and children	LOAEL=50 mg/kg/day UF = 300 <b>Acute RfD</b> = 0.17 mg/kg/day	FQPA SF = 10 for infants and children FQPA SF=1 general pop. <b>aPAD</b> = <u>acute RfD</u> FQPA SF = 0.017 mg/kg/day (infants and children) = 0.17 (general pop.)	Single Dose Rat Study (Nakai et al. 1992) LOAEL= 50 mg/kg/day based on adverse testicular effects including sloughing (premature release) of immature germ cells 2 days post exposure, atrophy of a few seminiferous tubules in one testicle, significant decrease in seminiferous tubule diameter, and slight abnormal growth of the efferent ductules at 70 days post exposure.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Chronic Dietary	NOAEL=2.5 mg/kg/day  UF = 100 <b>Chronic RfD</b> = 0.025 mg/kg/day	FQPA SF = 10 for children and females 13-50 yrs FQPA SF=1 general pop. <b>cPAD</b> = <u>chronic RfD</u> FQPA SF = 0.0025 mg/kg/day (children and females) = 0.025 (general pop.)	2 year dog study with MBC LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes.
Short-Term Incidental Ingestion	Oral NOAEL =10 mg/kg/day	<b>LOC for MOE = 300</b> for all residential populations <b>LOC for MOE = 100</b> for occupational workers	1997 Rabbit Developmental Study with thiophanate-methyl** LOAEL= 20 mg/kg/day based on decreased maternal body weight and food consumption.
Intermediate-Term Incidental Ingestion	Oral NOAEL =11 mg/kg/day (rounded to 10 mg/kg/day)	<b>LOC for MOE = 300</b> for all residential populations	90 day dog feeding study with MBC LOAEL= 35 mg/kg/day based on adverse liver effects.
Short-and Intermediate Term Dermal (a)	Oral NOAEL =10 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	<b>LOC for MOE = 1000</b> for children and females (residential) <b>LOC for MOE = 100</b> for occupational workers	Rat Developmental Study with MBC LOAEL= 20 mg/kg/day based on decreased fetal body weight and increases in skeletal variations and a threshold for malformations in fetuses of exposed dams
Long-Term Dermal (a)	Oral NOAEL =2.5 mg/kg/day (dermal absorption rate = 3.5% relative to oral absorption)	<b>LOC for MOE = 100</b> for occupational workers	2 year dog study with MBC LOAEL= 12.5 mg/kg/day based on histopathological lesions of the liver characterized as swollen, vacuolated hepatic cells, hepatic cirrhosis and chronic hepatitis in both sexes of dogs.
Short-, Intermediate- and Long Term Inhalation	Inhalation NOAEL= 0.96 (10 mg/m <sup>3</sup> )	<b>LOC for MOE = 1000</b> for children and females (residential) <b>LOC for MOE = 100</b> for occupational workers	90 day rat inhalation study with benomyl*** LOAEL= 4.8 mg/kg/day (50 mg/m <sup>3</sup> ) based on Olfactory degeneration in the nasal cavity
Cancer (a)	Q1* = 2.39x10 <sup>-3</sup> (mg/kg/day) <sup>1</sup> (dermal absorption rate =3.5% relative to oral absorption; inhalation absorption rate=100% relative to oral absorption)	Q1* = 2.39x10 <sup>-3</sup> (mg/kg/day) <sup>1</sup>	2 year mouse study with MBC based on hepatocellular (adenoma and/or carcinoma) tumors in female CD-1 mice

\* The reference to the FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.

\*\* Thiophanate-methyl was selected as a surrogate for short-term incidental oral exposure because 1) no applicable MBC data were available and 2) all incidental oral exposure would come from thiophanate-methyl uses exclusively, as benomyl has no residential uses.

\*\*\* Benomyl is used as a surrogate because MBC is the primary metabolite of benomyl and both compounds exhibit identical

toxic effects.

UF = Uncertainty Factor

PAD = Population Adjusted Dose (includes UF and FQPA safety factor)

LOC= Level of Concern

MOE = Margin of Exposure

(a) Since an oral value was selected, a 3.5% dermal absorption factor (based on a benomyl rat study) was used for route-to-route extrapolation.

The Uncertainty Factor (UF) used in the dietary and residential risk assessments for ***thiophanate-methyl*** is 300 to account for both interspecies extrapolation (10X) and intraspecies variability (10X) as well as a 3X FQPA Safety Factor for the protection of infants and children. The FQPA Safety Factor was retained at 3X due to an incomplete toxicity database; acute and subchronic neurotoxicity studies are required due to evidence of neurotoxicity (tremors) in the chronic dog study. However, the full 10X FQPA factor was not considered necessary because the available data provided no indication of increased susceptibility in the developmental studies in rats and rabbits or following pre-/postnatal exposure in the multi-generation reproduction studies in rats; and the dietary (food and drinking water) and non-dietary exposure assessments will not underestimate the potential exposures for infants and children from the use of thiophanate-methyl. The 3X FQPA safety factor is applicable to the acute/chronic dietary and residential risk assessments for all population subgroups.

For ***MBC***, the full 10X FQPA safety factor was retained for all risk assessments (acute/chronic dietary and residential scenarios). The rationale for retention of the 10X FQPA Safety Factor is: (i) there is evidence of increased susceptibility to offspring following *in utero* exposure to MBC in the prenatal developmental toxicity studies in rats and rabbits; and (ii) a developmental neurotoxicity study in rats is required for MBC due to the neurotoxicity seen in the benomyl acute and subchronic neurotoxicity studies in adult rats, the central nervous system anomalies in fetuses seen in the benomyl prenatal developmental toxicity study in rats, and the developmental central nervous system malformations seen in fetuses in the prenatal developmental toxicity study for MBC. The 10X FQPA safety factor is applicable to Females 13-50 since increased susceptibility was demonstrated following *in utero* exposure, and to Infants and Children (1-6 years and 7-12 years) due to the uncertainty resulting from the need for a developmental neurotoxicity study in rats.

### ***Dietary (Food) Risk Assessments for Thiophanate-methyl and MBC***

The residues of concern in plant commodities for use in the dietary exposure assessments include thiophanate-methyl as well as the metabolites MBC and 2-Aminobenzamidazole (2-AB). No endpoints have been determined for 2-AB; consequently it is assumed that 2-AB has an equivalent toxicity to MBC on a gram/gram comparative basis. The residues of concern in livestock commodities are thiophanate-methyl, MBC, 4-OH-MBC, 5-OH-MBC, and 5-OH-MBC-S. The hydroxylated metabolites are also considered equivalent to MBC for toxicological consideration. **For the purposes of this document, all dietary risk assessments performed on the sum of the metabolites will refer only to MBC.**

For plant commodities, the dietary risk assessments were conducted primarily using anticipated residues from field trial studies in combination with data from nature of residue studies on four crops (see Appendix A). Adjustment factors were used to extrapolate the ratios from these four crops to all other registered plant uses, which adds some uncertainty to the exposure estimates. For animal commodities, residues were estimated using field trial data for livestock feed items combined with livestock feeding studies. No monitoring data from the USDA Pesticide Data Program (PDP) and the FDA Surveillance monitoring program were available for thiophanate-methyl.

The use of field trial data is considered conservative because field trial data typically reflect treatment at the maximum application rate, and harvest at the minimum pre-harvest interval (PHI). Also, field trial data assume no residue decline between harvest and consumption of the crop. Additional uncertainty also arises from the use of field trial data because the data do not reflect residues potentially present at the time of consumption. For example, the risk assessments for thiophanate-methyl assume that all residues have structures closely related to the parent compound. In reality, more MBC and less thiophanate-methyl may be present in food at the time of consumption since thiophanate-methyl degrades to MBC over time. Monitoring data, processing studies (cooking/canning/washing) and market basket survey data could be used to further refine the assessments.

The dietary exposure analyses are based on the Dietary Exposure Evaluation Model (DEEM™) and percent of crop treated data. The DEEM™ analysis reflects individual food consumption as reported by respondents in the USDA 1989-92 Continuing Surveys for Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. Default processing factors from DEEM were incorporated into the dietary exposure analyses where appropriate. Usage data were not available for onions and potatoes so 100% crop treated was assumed.

### ***Acute Dietary (Food) Risk***

Acute dietary risk is calculated considering both daily consumption and residue values in the food. The Agency uses a probabilistic technique (Monte Carlo) so that the high-end and low-end consumer have an equal chance of getting a high or low residue value. A risk estimate that is less than 100% of the acute Population Adjusted Dose (aPAD) (the dose at which an individual could be exposed on any given day that would not be expected to result in adverse health effects) does not exceed the Agency's level of concern. The acute dietary risk assessments for thiophanate-methyl and MBC were conducted using average residues from field trials in combination with data from nature of residue studies and maximum percent crop treated estimates.

For *thiophanate-methyl*, the acute dietary (food) risk does not exceed the Agency's level of concern (>100% aPAD) for the U.S. population and all subgroups. The most highly exposed population subgroup is infants, whose dietary exposure is calculated to be 21% of the aPAD.

For *MBC*, the acute dietary risk assessment indicates that at the 99.9th percentile of exposure,

the acute dietary risk estimates are below the Agency's level of concern (<100% aPAD for the U.S. population and all population subgroups **except** infants (108% aPAD). A critical exposure analysis showed canned peaches as the major contributor (70%) for infants.

Risk estimates for *thiophanate-methyl* and *MBC* were added together for females (13-50 years) to account for total risk estimates for developmental effects. This is considered appropriate because both chemicals have aPADs that are based on similar developmental effects, and because individuals may consume both residues simultaneously on a given food commodity. The dietary risks for thiophanate-methyl and MBC were not combined for children or the general population because the aPADs are based on different effects (i.e., tremors for thiophanate-methyl, and testicular effects for MBC). Using the toxic equivalency factor (TEF) approach, all thiophanate-methyl dietary exposure estimates were adjusted downwards to account for the differences in aPADs between thiophanate-methyl and MBC (i.e., the aPAD is 0.067 mg/kg/day for thiophanate-methyl, but 0.01 mg/kg/day for MBC, therefore, a factor of 0.15 was applied to the thiophanate-methyl dietary estimate). As shown in Table 3, this approach is identical to summing the %aPAD for thiophanate-methyl and the %aPAD for MBC. The total dietary risk estimate for thiophanate-methyl and MBC is 58% of the aPAD and is below EPA's level of concern for females (13-50 years).

**Table 3. Tier 3 Acute Dietary Exposure and Risk Summary (99.9th Percentile of Exposure)**

Population	Thiophanate-methyl Estimate		MBC Estimate (from Thiophanate-methyl)		Thiophanate-methyl and MBC	Total Risk Estimate for Thiophanate-methyl and MBC
	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Total Exposure in MBC Equivalents (mg/kg/day)	% aPAD
U.S. Population	0.011375	8.6	0.006838	4	NA	NA
All Infants <1 year	0.02847	21.4	0.018429	108	NA	NA
Children 1-6 years	0.021471	16.1	0.013911	81.8	NA	NA
Children 7-12 years	0.01379	10.4	0.008852	52	NA	NA
Females 13-50	0.006729	10	0.004756	47.6	0.00576	57.6

### ***Chronic Dietary (Food) Risk***

Chronic dietary risk over a 70-year lifetime is calculated using average residues from field trials in combination with data from nature of residue studies and weighted average percent crop treated data. A risk estimate that is less than 100% of the chronic Population Adjusted Dose (cPAD) (the dose at which an individual could be exposed over the course of a lifetime and no adverse health effects would be expected) does not exceed the Agency's risk concern.

For *thiophanate-methyl*, the chronic dietary risk from food is significantly below the Agency's level of concern, i.e., less than 100% of the cPAD is utilized, for all population subgroups. The most exposed subgroups are infants (<1 year) and children (1-6 years), with an estimated exposure corresponding to 1% of the cPAD.

For *MBC*, chronic dietary risk estimates are below the Agency's level of concern (<100% cPAD) for the U.S. population and all population subgroups. The most highly exposed population subgroup is children 1-6 years old with 20% of the cPAD consumed.

Similar to the acute dietary risks, a total dietary risk estimate was calculated for thiophanate-methyl and MBC. In this case, a total dietary estimate could be calculated for all subpopulations due to similar adverse (liver) effects<sup>2</sup>. Using the TEF approach, the thiophanate-methyl dietary exposure estimates were adjusted downwards to account for the differences in cPADs between thiophanate-methyl and MBC (i.e., general population cPAD is 0.027 mg/kg/day for thiophanate-methyl, but 0.025 mg/kg/day for MBC, therefore, a factor of 0.93 was applied to the thiophanate-methyl dietary estimate). This approach is identical to summing the %cPAD for thiophanate-methyl and the %cPAD for MBC. As shown in Table 4, the highest total dietary risk estimate is 21% for children 1-6 years, which is below the Agency's level of concern.

**Table 4. Chronic Dietary Exposure and Risk Summary**

Population Subgroup	Thiophanate-methyl		MBC (from Thiophanate-methyl)		Thiophanate-methyl and MBC	Total Risk for Thiophanate-methyl and MBC
	Exposure (mg/kg/day)	%cPAD	Exposure (mg/kg/day)	%cPAD	Total Exposure in MBC Equivalents (mg/kg/day)	%cPAD
US Population	0.000109	0.4	0.000163	0.7	0.000264	1.1
All infants (< 1 yr)	0.000329	1.2	0.000343	13.7	0.000373	15
Children (1-6 years)	0.000262	1	0.000501	20	0.000526	21
Children (7-12 years)	0.000171	0.6	0.000294	11.8	0.00031	12
Females 13-50	0.000075	0.3	0.00012	4.8	0.000127	5.1

<sup>2</sup>Although the cPAD for thiophanate-methyl is based specifically on thyroid effects, the liver is a primary target organ of this chemical. In addition, in the chronic dog and rat studies, there is only minor difference between the 40 and 54 mg/kg/day LOAELs for thyroid and liver effects respectively, where the corresponding NOAELs were 8 and 8.8 mg/kg/day respectively.

## ***Carcinogenic (Food) Risk, Thiophanate-methyl and MBC***

***Thiophanate-methyl*** is classified as "likely to be carcinogenic to humans" based on liver cell tumors in mice; therefore, a cancer dietary risk assessment using a low-dose linear extrapolation was conducted. The cancer risk from food due to thiophanate-methyl exposure is  $1.5 \times 10^{-6}$  which is marginally above the Agency's level of concern (i.e.,  $1.0 \times 10^{-6}$ , or 1 in 1 million) for carcinogenic risk.

***MBC*** is classified as a Group C (possible human) carcinogen based on liver tumors in mice. A cancer dietary risk assessment using a low-dose linear extrapolation was conducted. The cancer risk from food due to MBC exposure is  $3.89 \times 10^{-7}$  which is below the Agency's level of concern (i.e.,  $1.0 \times 10^{-6}$ ) for carcinogenic risk.

It is appropriate to add the cancer risk estimates from ***thiophanate-methyl and MBC*** because both chemicals cause mouse liver tumors, and because both chemicals are found concurrently on food items treated with thiophanate-methyl. Using the TEF approach, the thiophanate-methyl dietary exposure estimates were adjusted upwards using a factor of 5.77 to estimate MBC equivalents. The total (i.e. sum of thiophanate-methyl and MBC) lifetime cancer risk estimate is  $2.0 \times 10^{-6}$ . This lifetime risk estimate for food alone is marginally above the level the Agency generally considers to be negligible for lifetime cancer risk (i.e.,  $1 \times 10^{-6}$ ).

## ***Drinking Water Dietary Risk***

Drinking water exposure to pesticides can occur through groundwater and surface water contamination. EPA considers both acute (one day) and chronic (lifetime) drinking water risks and uses either modeling or actual monitoring data, if available, to estimate those risks. To determine the maximum allowable contribution of treated water allowed in the diet, EPA first looks at how much of the overall allowable risk is contributed by food, then determines a "drinking water level of comparison" or DWLOC. The DWLOCs represent the maximum contribution to the human diet (in : g/L or ppb) that may be attributed to residues of a pesticide in drinking water after dietary exposure is subtracted from the aPAD or cPAD. Risks from drinking water are assessed by comparing the DWLOCs to the estimated environmental concentrations (EECs) in surface water and ground water. The Agency generally has no risk concerns when the EECs are below the DWLOCs. Note that for thiophanate-methyl, DWLOCs are calculated from food exposure estimates derived from field trial data, which the Agency considers conservative.

- The rapid rate of degradation of thiophanate-methyl to the primary degradate MBC on foliage and in water along with the persistence of MBC in water are key factors that influence acute and chronic risks to humans from ingestion of drinking water. Since thiophanate-methyl rapidly degrades to MBC, the drinking water assessment was conducted on thiophanate-methyl as well as its principal degradate, MBC. Thiophanate-methyl and MBC have the potential to enter surface waters by erosion of soil particles to which these chemicals are adsorbed or via

dissolution in runoff water, especially in areas with large amounts of annual rainfall that could result in large volumes of runoff. MBC has a low potential to leach to groundwater in measurable quantities based on its high soil organic carbon partition coefficient (K<sub>oc</sub>) of 2,100 l/kg.

- The Agency currently lacks sufficient water monitoring data to complete a quantitative drinking water exposure analysis. In the absence of monitoring data, EPA used models to calculate the EECs. The primary use of these models by the Agency is to provide a screen for assessing whether a pesticide could be present in drinking water at concentrations that would exceed human health levels of concern.
- The modeling was conducted based on the environmental profile and the maximum seasonal application rate for thiophanate-methyl use on ornamentals, turf, and onions; the use sites expected to provide the highest environmental exposures resulting from thiophanate-methyl use.
- Generic Estimated Environmental Concentrations (GENEEC), a Tier I model, was used to predict EECs for thiophanate-methyl and MBC in surface water for turf and ornamentals. Currently, a more refined model is not available to estimate EECs from turf/ornamental application. The EECs derived from GENEEC are considered to be upper-bound.
- PRZM/EXAMS, a Tier II model, was used to estimate concentrations of thiophanate-methyl and MBC in surface water from application to onions. PRZM/EXAMS is considered a more refined model than GENEEC.
- The Screening Concentration in Ground Water (SCI-GROW), a Tier I model, was used to predict EECs for thiophanate-methyl and MBC in ground water for all modeled use sites. Currently, there is no Tier II assessment tool for groundwater.

DWLOCs are based on simultaneous dietary exposure to both thiophanate-methyl and MBC (as MBC equivalents) in those cases where endpoints are based on similar toxic effects (i.e. females 13+ acute food exposure values and chronic/cancer food exposure values for all subpopulations). Values for other populations are based on MBC alone<sup>3</sup> due to different endpoints.

Since the estimated concentrations of thiophanate-methyl and MBC individually in drinking water are already of concern compared to the DWLOC, the EECs were not combined using a TEF approach, but instead are presented separately. The results of the drinking water assessment for thiophanate-methyl and MBC are summarized in Table 5 (turf/ornamentals) and Table 6 (onions).

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<sup>3</sup>MBC alone, rather than thiophanate-methyl alone, was selected to calculate the DWLOCs in those cases where exposure estimates could not be added because MBC consistently resulted in higher risk estimates.

**Table 5. Drinking Water DWLOC and EEC Comparisons for Thiophanate-methyl and MBC on Turf/Ornamentals**

Population Subgroup	MBC DWLOCs (ppb) <sup>1</sup>			EECs (ppb) for turf/ornamentals		
	Acute	Chronic	Cancer	Ground Water (SCI-GROW)	Surface Water (GENEEC)	
					Acute	Chronic and Cancer
U.S. Population	5,700	850	zero (no room)	3.03/15 (MBC)	320/1,600 (MBC)	50/243 (MBC)
All Infants (< 1Year)	zero (no room)	21	N/A	0.033/0.17 (TM)	420/2,100 (TM)	73.3/367 (TM)
Children (1-6 years)	31	20	N/A			
Females (13-50 years)	130	71	N/A			

<sup>1</sup> DWLOC values are based on MBC alone due to different endpoints except for Females 13-50 where MBC and TM exposure estimates were added. Chronic DWLOC values represent the sum of thiophanate-methyl and MBC dietary exposure. “Zero” means that there is no room available for additional exposure through drinking water because the food exposure alone already exceeds the level of concern.

**Table 6. Drinking Water DWLOC and EEC Comparisons for Thiophanate-methyl and MBC on Onions**

Population Subgroup	MBC DWLOCs (ppb) <sup>1</sup>			EECs (ppb) for onions		
	Acute	Chronic	Cancer	Ground Water (SCI-GROW)	Surface Water (PRZM-EXAMS)	
					Acute	Chronic and Cancer
U.S. Population	5,700	850	zero (no room)	0.51 (MBC)	210 (MBC)	73.5 (MBC)
All Infants (< 1Year)	zero (no room)	21	N/A	0.006 (TM)	50 (TM)	.440 (TM)
Children (1-6 years)	31	20	N/A			
Females (13-50 years)	130	71	N/A			

<sup>1</sup> Acute DWLOC values are based on MBC alone due to different endpoints except for Females 13-50 where MBC and TM exposure estimates were added. Chronic DWLOC values represent the sum of thiophanate-methyl and MBC dietary exposure. “Zero” means that there is no room available for additional exposure through drinking water because the food exposure alone already exceeds the level of concern.

### **Drinking Water - Acute Dietary Risk from Thiophanate-methyl/MBC**

As shown in Tables 5 and 6, acute exposure to thiophanate-methyl and MBC in food + water exceeds the EPA’s level of concern for infants, children (1-6 years) and females (13-50 years). The

acute DWLOC is effectively zero for infants (<1 year old) because the acute dietary exposure to MBC alone exceeds the Agency's level of concern (i.e., >100% aPAD). Therefore, potential drinking water exposures will only further contribute to exposures of concern for this subpopulation. For children (1-6 years) and females of child bearing age (13-50 years) the acute EECs for surface water (but not groundwater) exceed the acute DWLOCs, indicating that food + drinking water may be of concern for these subpopulations.

### **Drinking Water - Chronic Dietary Risk from Thiophanate-methyl/MBC**

As shown in Tables 5 and 6, the DWLOCs for Infants, Children and Females 13+ are less than the EECs for surface water. Therefore, for these subpopulations, chronic food + drinking water exposure to thiophanate-methyl and MBC exceeds the Agency's level of concern based on the screening-level model. Surface water, rather than ground water, is of concern, as all DWLOCs are greater than the groundwater EECs.

### **Drinking Water - Carcinogenic Risk from Thiophanate-methyl/MBC**

- The dietary (food) cancer risk to thiophanate-methyl and MBC alone ( $2.0 \times 10^{-6}$ ) already exceeds the Agency's level of concern of  $1.0 \times 10^{-6}$ . Consequently, the DWLOC is effectively zero and any additional water exposure will further contribute to potential risks of concern.

### ***Non-dietary (Residential/Public) Risks from Thiophanate-methyl Uses***

Potential exposures are anticipated as a result of homeowner and commercial applications in residential areas. Applications can be made to lawns, ornamentals and "backyard" orchards<sup>4</sup>. In addition to residential areas, there are also potential postapplication exposures scenarios that may occur in public areas such as parks, recreational areas and golf courses.

In general, most of the residential scenarios for both non-cancer and cancer health risks exceed EPA's levels of concern. Specifically, children playing on lawns, adults spraying lawns, and adults/youths picking treated fruit at home, all had risk estimates which exceed the levels of concern. Only the lower-contact activities, such as mowing, golfing, or using a push-spreader to apply granular formulations consistently had risks below EPA's level of concern.

For thiophanate-methyl, short- and intermediate-term dermal and inhalation endpoints are based on the same toxicological effects, and therefore risks from dermal and inhalation exposure are added together in the residential assessment. For MBC, the short- and intermediate-term dermal and inhalation

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<sup>4</sup>Only postapplication exposures to backyard orchards are evaluated as current labels only permit professional treatments to home orchards.

toxicity endpoints are different so risk estimates from dermal and inhalation exposures are presented separately.

Because the toxicological non-cancer endpoints for MBC and thiophanate-methyl are different for short- and intermediate-term dermal and inhalation exposures, the estimated risks from the different chemicals are not added together in the residential assessment. The cancer risk estimates may be added, however, as both chemicals produce liver tumors. See Tables 1 and 2 for a summary of the toxicological endpoints and doses that were used to complete the non-dietary risk assessment.

As noted previously, the FQPA safety factor was retained at 3X for all thiophanate-methyl residential risk assessments due to an incomplete toxicological database, raising the Agency's level of concern (i.e., target MOE) to 300. For MBC, the residential target MOE is 1,000 due to an additional 10x FQPA factor for increased fetal susceptibility and lack of a developmental neurotoxicity study. Residential cancer risk estimates less than  $1.0 \times 10^{-6}$  do not exceed the Agency's level of concern for either chemical.

### **Residential Handler Risk Estimates**

MBC residues are initially very low relative to thiophanate-methyl and only approach the level of the parent several days to weeks (if ever) after application. Therefore, MBC exposure is not anticipated during residential handler tasks. Only short-term (less than 7 days) dermal and inhalation exposures are anticipated for residents applying thiophanate-methyl products. In addition to short-term non-cancer risk, cancer risks to residential handlers were assessed.

The residential handler assessment used the revised "Standard Operating Procedures (SOPs) for Residential Exposure Assessment" as well as surrogate data from the Pesticide Handler Exposure Database (PHED) and the Outdoor Residential Exposure Task Force (ORETF) for some scenarios. The Residential SOPs are considered to be conservative scenarios for determining risk estimates. Since the toxicological effects from dermal exposures are similar to those from inhalation exposures, dermal and inhalation exposures are combined in this assessment.

The following scenarios were evaluated for residential handler lawn/garden application:

- 1a) Applying with a ready-to-use hose-end sprayer
- 1b) Mixing, loading/applying liquid with a hose-end sprayer
- 2) Mixing/loading/applying wettable powders with a low pressure wand
- 3) Mixing/loading/applying liquids with a low pressure wand
- 4) Mixing/loading/applying liquids with a backpack sprayer
- 5) Loading/applying with a push-type spreader
- 6) Loading/applying with a belly grinder
- 7) Hand dispersal of granules (spot treatment)

The risk assessment indicates that total **non-cancer** risks to residential handlers exceed EPA's level of concern for four of the scenarios involving application to lawns (target MOE = 300).

- C mixing, loading, and applying liquid with a hose-end sprayer (MOE = 84),
- C mixing/loading/applying liquid (MOE = 190) and wettable powder (MOE = 72) formulations with a low pressure (pump) handwand sprayer,
- C loading/applying granular formulation with a bellygrinder (MOE = 230), and
- C hand dispersal of granules (MOE = 58).

Total exposures for residents applying thiophanate-methyl granular formulations via push-spreader or liquid formulations by hose-end sprayer (ready to use) did not exceed EPA's level of concern. Likewise, exposures while applying thiophanate-methyl to ornamentals by spreader or sprayer did not exceed the level of concern because a smaller area is assumed to be treated. Inhalation exposure contributes significantly less to risk than dermal exposure.

Lifetime **cancer** risk estimates for applying thiophanate-methyl formulated products range from  $5.2 \times 10^{-9}$  to  $4.5 \times 10^{-6}$ . Two scenarios have cancer risk estimates that exceed  $1 \times 10^{-6}$ :

- Mixing/loading/applying liquids with a hose-end sprayer at the maximum rate for broadcast lawn treatment ( $4.5 \times 10^{-6}$ ), and
- Hand dispersal of granules for a spot treatment ( $3.2 \times 10^{-6}$ ).

### **Residential Postapplication Risk Estimates**

Short-/intermediate-term non-cancer risks and cancer risks from residential postapplication exposures were estimated for thiophanate-methyl and for its degradate, MBC. Two groups, adults and children, are potentially exposed to residues after application of thiophanate-methyl products in residential settings. No long-term (six months or more) residential exposures are associated with the use of thiophanate-methyl due to the use pattern and dissipation rate. Only potential dermal exposures were considered because all activities were outdoors for homeowners and the vapor pressure of MBC is very low. Residential postapplication risk estimates utilized residue dissipation studies and a turf transfer study, as well as the EPA's original and revised "SOPs for Residential Exposure Assessment".

The following residential postapplication scenarios were evaluated:

- 1) Dermal exposure to adults and adolescents (10–12 years) involved in low-moderate exposure activities, such as golfing, walking, or mowing on treated turf;
- 2) Dermal exposure to adults and young children involved in a high exposure activity, such as heavy yard work or playing on treated turf;
- 3) Incidental oral exposure to children (1-6 years) playing on treated turf from turf mouthing, hand to mouth, granular ingestion, and incidental soil ingestion.
- (4) Dermal exposure to adults, and adolescents involved in harvesting treated fruit in a home orchard.

Exposure scenarios with *non-cancer risk estimates for thiophanate-methyl* that exceed the Agency's level of concern (i.e., MOEs <300) include:

- children playing on treated lawns (MOEs of concern range from 9 to 240)
- adults involved in high dermal contact activities such as hand weeding (MOEs range from 140-240)
- adults picking fruit at home (MOE of concern is 210).

All postapplication risk estimates for *MBC* were above 1000, and therefore do not exceed EPA's level of concern. Post-application *cancer risk estimates for combined thiophanate-methyl and MBC exposures* are not of concern except for dermal exposure during fruit harvesting ( $1.2 \times 10^{-6}$  to  $3.7 \times 10^{-6}$ ).

### ***Non-dietary Risks from MBC Uses***

MBC is used as a fungicide/preservative in paints, coatings, plaster and adhesives. However, there were only three scenarios for which surrogate exposure data were available: applying paints by brush, low-pressure handwand and airless sprayer. Exposure from paint roller application or to other types of treated products could not be estimated.

Although there were no chemical-specific data for any of the residential handler scenarios, PHED data from painting exposure studies are believed to be similar to the three assessed scenarios and the surrogate data were of medium-to-high confidence level. For indoor settings, it was assumed that 2 gallons of paint or coating could be applied per day. For applying paint/coating with an airless sprayer to the exterior of a home, the amount handled was assumed to be 2,800 ft<sup>2</sup> (area treated). Residential applicators are anticipated to apply paint or coatings 4 days per year (cancer risk estimates). Dermal and inhalation margins of exposure (MOEs) are presented separately due to the different endpoints selected. Residential handlers are anticipated to have only short-term (one week or less) dermal and inhalation exposures to MBC as a fungicidal additive in ready-to-use products.

Postapplication exposure to MBC-treated paints, coatings, and sealants is anticipated to be only by the inhalation route, as the treated materials will have dried and have low potential for dermal transfer. The Multi-Chamber Concentration and Exposure Model (MCCCEM) was used to estimate post application inhalation exposures for occupants of a house after painting one room. The modeled air concentration in the unpainted portion of the house was used to estimate occupant exposure over the course of a year. The residential postapplication risk estimates for the MBC paint use are believed to be conservative because users are unlikely to be exposed 365 days per year nor are they likely to repaint the same rooms annually. Also, MBC has a very low vapor pressure and MBC-containing products are only intended for use in damp areas such as bathrooms or basements.

**Residential Handler Risk Estimates:** For the three painting scenarios assessed, all *dermal non-*

*cancer* risks exceeded EPA's level of concern (target MOE = 1000) for non-occupational handlers, with dermal MOEs ranging from 620-750. *Inhalation* exposure was not of concern except for painting with an airless sprayer (inhalation MOE = 230). All *cancer* risk estimates for residential handlers were less than  $1 \times 10^{-6}$  and are therefore not of concern.

**Residential Postapplication Risk Estimates:** Postapplication *non-cancer* inhalation risks for toddlers and adults are well below EPA's level of concern (MOEs = 1,100,000 and 4,600,000 respectively). The *cancer* risk estimate for the same scenario is  $3.6 \times 10^{-10}$ . Although the occupant's exposure during application, described in the previous section, would be additive to their postapplication exposure, the total cancer risk is still below the Agency's level of concern of one in one million.

## ***Aggregate Risk***

The aggregate risk assessment includes combined exposure from food, drinking water, and non-dietary (residential/public) uses. In all, five aggregate risk assessments were considered or conducted: acute (1 day), short-term (1-7 days), intermediate-term (7 days to several months), chronic (several months to lifetime), and cancer (several months to lifetime).

The aggregate assessments were conducted or considered under two scenarios: (1) thiophanate-methyl and MBC exposures resulting *exclusively* from thiophanate-methyl uses and, (2) exposure to thiophanate-methyl and MBC from thiophanate-methyl uses *in addition to* registered MBC paint uses.

**Table 7. Aggregate Assessments Under Scenario I and II**

	Exposures considered	Scenario I	Scenario II
Acute	Food + water	DWLOC based on dietary exposure to MBC. <sup>1</sup> EECs for both TM and MBC presented (not combined). <sup>2</sup> For Females 13-50, DWLOC based on dietary exposure to TM and MBC combined. <sup>3</sup>	Same as acute aggregate I.

	Exposures considered	Scenario I	Scenario II
Short-term	Food, water, residential	Residential exposures to thiophanate-methyl alone result in MOEs that exceed EPA's level of concern. If conducted, the following uses would be aggregated with chronic thiophanate-methyl and MBC dietary exposure: oral and dermal exposure to treated turf, dermal exposure from fruit harvest, and handler dermal exposure during broadcast application. <sup>4</sup>	Residential exposures to thiophanate-methyl alone result in MOEs that exceed EPA's level of concern. If conducted, the aggregate assessment would contain the same exposures as listed in scenario I plus dermal and inhalation exposure to MBC during paint application. <sup>4</sup>
Intermediate-term	Food, water, residential	Same as short-term aggregate I	Same as short-term aggregate II.
Chronic	Food + water	EECs for both thiophanate-methyl and MBC presented. <sup>2</sup> DWLOC based on dietary exposure to thiophanate-methyl and MBC combined. <sup>3</sup>	Same as chronic aggregate I. <sup>5</sup>
Cancer	Food, water, residential	Not conducted because chronic dietary exposure to thiophanate-methyl and MBC on food alone exceed EPA's level of concern ( $> 1 \times 10^{-6}$ ). If conducted, would include chronic dietary exposure from thiophanate-methyl and MBC residues estimated in food and water, and dermal exposures from the following residential uses of thiophanate-methyl: broadcast lawn treatment, postapplication lawn exposure, and fruit harvesting. <sup>4</sup>	Not conducted because chronic dietary exposure to thiophanate-methyl and MBC on food alone exceed EPA's level of concern ( $> 1 \times 10^{-6}$ ). If conducted, would include the same exposures as listed in scenario I plus MBC exposure to both the residential handler during paint activities and to vapors following painting. <sup>4</sup>

1 MBC alone, rather than thiophanate-methyl alone, was selected to calculate the DWLOCs in those cases where exposure estimates could not be added because MBC consistently resulted in higher risk estimates.

2 Since the estimated concentrations of thiophanate-methyl and MBC individually in drinking water are already of concern compared to the DWLOC, the EECs were not combined, but instead are presented separately.

3 Converted to MBC equivalents. The DWLOCs were then estimated using the aPAD or cPAD for MBC.

4 Although exposures from multiple sources would be evaluated, only risk estimates associated with common toxicological endpoints would be aggregated. Also, exposures would be aggregated based on the subpopulation and EPA's judgement regarding what is considered reasonable to aggregate.

5 While there are potentially chronic inhalation exposures to MBC vapors from use of MBC as a paint additive, these exposures were not considered in the non-cancer aggregate assessment because the endpoint of concern (respiratory effects) is different from the chronic oral endpoint of concern (liver effects). However, inhalation exposure from MBC vapors was included in the cancer aggregate assessment.

The aggregate assessments are considered somewhat conservative because: (1) the dietary exposure analysis was based on field trial data residues, (2) the drinking water EECs were calculated using screening-level models which do not reflect dilution from source to tap or water treatment, and (3) the risk estimates for MBC use as a paint additive are based on high end assumptions for occupancy and air exchange rates, and assume no degradation or matrix effects<sup>5</sup> of the paint. However, risks from thiophanate-methyl residential uses aren't considered worst-case since only a few, select residential scenarios were aggregated with dietary exposure.

**Acute Aggregate Risk, Thiophanate-methyl Use Only:** The acute aggregate risk assessment addresses exposure solely from food and drinking water (only short- and intermediate-term residential exposure is anticipated). As described in the drinking water section, acute aggregate exposure to MBC (and thiophanate-methyl for females 13-50) in food and water exceeds the Agency's level of concern for infants, children (1-6 years) and females (13-50 years). For infants, acute food exposure to MBC alone exceeds the Agency's level of concern.

**Short- and Intermediate-term Aggregate Risk, Thiophanate-methyl Use Only** Short- and intermediate-term aggregate exposure takes into account chronic dietary food and water (considered to be a background exposure level) plus short- and intermediate-term dermal and inhalation exposure from residential and other non-occupational settings. In this case, short- and intermediate-term aggregate risk estimates were not calculated for thiophanate-methyl/MBC because many of the non-occupational exposures for both residential handlers and during post application activities already exceed the Agency's level of concern. Any additional short-term exposures through food and drinking water would result in risks that would further exceed the Agency's level of concern.

**Chronic Aggregate Risk, Thiophanate-methyl Use Only** The aggregate chronic dietary risk estimates include exposure to thiophanate-methyl and MBC residues in food and water. As stated previously, the total dietary exposure to thiophanate-methyl and MBC for the highest exposed population subgroup, children 1-6 years, is 21% of the cPAD. However, the DWLOCs for Infants, Children and Females 13+ are less than the EECs for surface water. Therefore, for these subpopulations, chronic food + drinking water exposure to thiophanate-methyl and MBC exceeds the Agency's level of concern based on the surface water screening-level models.

**Cancer Aggregate Risk, Thiophanate-methyl Use Only** The total thiophanate-methyl and MBC dietary (food) cancer risk estimate is  $2 \times 10^{-6}$  for a 70 year exposure to the general U.S. population. This cancer risk estimate exceeds the level of concern of  $1 \times 10^{-6}$ . In addition, cancer risk estimates associated with some residential scenarios of thiophanate-methyl also exceed EPA's level of concern.

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<sup>5</sup> Constituents in paint that can bind MBC and prevent vaporization

**Short-term Aggregate Risk, Thiophanate-methyl and MBC From All Uses.** The short-term aggregate risk assessment includes average (chronic) MBC dietary exposure (food and water) from thiophanate-methyl uses, and short-term residential exposures to MBC (from thiophanate-methyl and MBC uses). Thiophanate-methyl *per se* exposures are aggregated for Females 13-50 due to similar toxic (developmental) effects and concurrent exposure to thiophanate-methyl and MBC on commodities and lawns treated with thiophanate-methyl.

As noted previously, most of the short-term exposures for both residential handlers and during post application activities result in risks of concern (MOEs less than 300) for thiophanate-methyl, and therefore already exceed EPA's level of concern based on a screening-level assessment using the residential SOPs. In addition, residential handler risks from MBC's use as a paint additive are also of concern. Therefore, any additional short-term exposures through food and drinking water would result in MOEs that further exceed the level of concern. Consequently, a short-term aggregate assessment for thiophanate-methyl and MBC from all uses is not presented.

**Intermediate-term Aggregate Risk, Thiophanate-methyl and MBC from All Uses.** Several of the intermediate-term residential post application exposures for children playing on treated lawns result in MOEs less than 300 for thiophanate-methyl, and therefore already exceed EPA's level of concern based on a screening-level assessment using the residential SOPs. Therefore, any additional intermediate-term-term exposures through food and drinking water would result in MOEs that would further exceed the level of concern. Consequently, an aggregate assessment for thiophanate-methyl and MBC from all uses was not conducted.

**Cancer Aggregate Risk, Thiophanate-methyl and MBC From All Uses.** For this assessment, aggregate exposures to MBC resulting from registered uses of thiophanate-methyl and MBC were evaluated. Chronic aggregate cancer exposure, includes all MBC chronic dietary exposure resulting from both thiophanate-methyl and MBC. In addition, thiophanate-methyl and MBC have the same toxic effects (i.e., liver effects), both have  $Q_1$ 's based on mouse liver tumors, and therefore were added together. Chronic residential exposures to MBC are not anticipated based on registered uses for thiophante-methyl. There are potential chronic inhalation exposures to MBC from MBC's registered use as a paint additive (i.e., dermal and inhalation exposures to a resident painter, and chronic inhalation to vapors in a painted room). Therefore, these MBC inhalation exposures were included in the aggregate risk estimates.

The aggregate cancer dietary risk estimates (food only) for MBC and thiophanate-methyl, combined is  $2 \times 10^{-6}$ . In addition, the total cancer risk estimates for thiophanate-methyl from dietary and some residential uses is  $9 \times 10^{-6}$ . The combined cancer risk estimate for combined thiophanate-methyl and MBC exposures from dietary and selected residential uses (i.e., lawn treatment and postapplication exposure) is  $1 \times 10^{-5}$ , primarily because of the residential exposures to thiophanate-methyl. These risk estimates exceed EPA's level of concern (i.e.  $1 \times 10^{-6}$ ).

## ***Occupational Risk***

Occupational handlers may be exposed to a pesticide through such tasks as mixing, loading, or applying a pesticide. Handler risk is measured by a Margin of Exposure (MOE) which determines how close the occupational handler exposure comes to a No Observed Adverse Effect Level (NOAEL). Generally, MOEs greater than 100 do not exceed the Agency's level of risk concern. For workers entering a treated site, restricted entry intervals (REIs) are calculated to determine the minimum length of time required before workers or others are allowed to enter. REIs are calculated in hours or days. See Tables 1 and 2 for a summary of the toxicological endpoints and doses that were used to complete the occupational risk assessment.

- **Annual Exposure Durations:** There is a potential for short- and intermediate-term exposures in occupational settings from handling thiophanate-methyl products or entering previously treated areas. For some use patterns, long-term exposures are anticipated based on very slow dissipation of foliar residues and, based on some labels, unlimited reapplications.
- **Levels of Concern:** MOEs greater than 100 do not exceed the Agency's level of concern for handlers and postapplication workers. For cancer risk, EPA attempts to mitigate occupational exposures so that risk estimates are one in one million ( $1 \times 10^{-6}$ ) or less.
- **Incidents.** A review of incident data sources found that relatively few incidents have been reported for thiophanate-methyl. However, the Agency does not have significant concerns for acute poisoning, which are the most likely to be reported, but rather chronic or developmental risk concerns. The majority of significant symptoms reported were respiratory or eye irritation, particularly when handling dry formulations. Other symptoms included shortness of breath, chest pains, burning eyes, dizziness, and fatigue. Spray and dust application methods were associated with the majority of the exposures.

### **Occupational Handlers:**

The handler risk assessment evaluated 25 major scenarios based on the use patterns and current labeling as well as the types of equipment and techniques that can be used to make thiophanate-methyl applications. The majority of analyses were performed using the *Pesticide Handlers Exposure Database* (PHED), Version 1.1. For treating seedlings by dipping, no exposure data are available to EPA and this scenario was not assessed. Only risks from thiophanate-methyl were evaluated; MBC exposure is not anticipated during handler tasks. The risk estimates from dermal and inhalation exposures are combined in these assessments. When available, the average or "typical" application rate was used for assessing cancer risks, since the assessment is based on a lifetime of exposure. Cancer risks were estimated for the various handler scenarios using two categories of handlers: private and commercial. EPA assumes that private handlers apply thiophanate-methyl less frequently than commercial handlers.

**Short-/Intermediate-term Risk Estimates for Occupational Handlers.** Overall, about half of the scenarios had MOEs of 100 at the baseline level of personal protection (long pants, long-sleeved shirt, shoes and socks). In general, with the addition of personal protection equipment (PPE), risks did not exceed the level of concern, *except* in a few instances when application rates exceed 10 pounds a.i. per acre. While the addition of gloves to baseline protection increased MOEs to > 100 for most (83%) of scenarios, adding respirators and coveralls only increased the number of scenarios with MOEs >100 to 90%. All MOEs were greater than 100 when engineering controls were added, where feasible. For mixing and loading wettable powder formulations to support aerial or chemigation applications, engineering controls (i.e., water-soluble packaging) are required for many crops and use-patterns. MOEs were less than 100 assuming maximum PPE for the highest application rate for loader/applicators using push-spreaders and belly grinders and no feasible engineering controls are available for these scenarios.

**Cancer Risk Estimates for Occupational Handlers.** At baseline, most of the exposure scenarios had estimated cancer risks between  $10^{-4}$  and  $10^{-6}$ . When PPE is added to scenarios with baseline cancer risk estimates greater than  $10^{-6}$ , risk estimates for private handlers ranged from  $5.5 \times 10^{-5}$  to  $1.2 \times 10^{-8}$ , and for commercial handlers from  $5.5 \times 10^{-4}$  to  $2.2 \times 10^{-7}$ . With the addition of engineering controls, where feasible controls exist, cancer risk estimates for all private handler scenarios were equal or less than  $10^{-6}$ , and estimates for commercial applicators ranged from  $2.9 \times 10^{-5}$  to  $1.1 \times 10^{-7}$ . Handler scenarios with high application rates (\$ 10 lbs ai/acre), very high acreage crops (1200 acres/day), or hand-held application equipment generally had cancer risk estimates greater than  $10^{-6}$ , even with the addition of PPE or engineering controls.

### **Postapplication Occupational Workers**

Occupational postapplication exposure can occur for agricultural workers during activities such as weeding, irrigation, pruning, harvesting, handling of seeds, seedlings, and seed pieces, etc. The current restricted entry interval (REI) for thiophanate-methyl is 12 hours. Both thiophanate-methyl and MBC postapplication exposures are anticipated, but these were not aggregated due to different toxic effects. Postapplication inhalation exposure is not assessed because it is expected to be negligible once sprays have settled based on the low vapor pressures of thiophanate-methyl and MBC ( $1.3 \times 10^{-5}$  mmHg and  $7.5 \times 10^{-10}$  mmHg respectively).

Three dislodgeable foliar residue (DFR) studies are available that address the dissipation of thiophanate-methyl as well as a study of turf transferable residues. Chemical-specific data were available to evaluate foliar transfer coefficients from a cut-flower worker study. For all other postapplication activities, the assessment relied upon standard Agency agricultural transfer coefficients. Data are not sufficient to characterize exposures to treated soil, treated seed or seedlings, or from sorting/packing treated vegetables in the field.

**Postapplication Risk Estimates for Occupational Workers:** For fruit/nut trees and woody ornamentals, the risk estimates are considerably higher when residue data from dry (western) versus

humid (eastern) climates are used. For these crops, an MOE of 100 is generally attained within one week for most activities when humid climate data are used, while one or two months were required to attain a MOE of 100 when dry climate data are used. For example, for thinning apples, a six day REI is necessary to reach the target MOE of 100 when residue data from a dry climate are used, however, 28 days are necessary to reach the target MOE when data from humid climate are used. Risk estimates are also higher when non-irrigated turf versus irrigated turf data were used. For example, high-contact activities on turf required 7 days to attain an MOE of 100 or more using non-irrigated turf data, but only 2 days using the irrigated turf data. Row crop reentry risk estimates indicated 1 day is sufficient to achieve an MOE of 100 for most tasks, except working with ornamentals. Cancer risk estimates for most activities on most crops are between  $10^{-4}$  and  $10^{-6}$ , although some high-contact activities exceed  $10^{-4}$ ; notably those involving cut flowers and woody ornamentals.

**Postapplication Risk Estimates for Occupational Workers from Exposures to MBC:** The risk assessment indicates that non-cancer risks to postapplication workers do not exceed the level of concern (MOE >100) from exposures to MBC residues. For short-/intermediate-term risks, the MOEs range from 250 to 630,000. Cancer risk estimates range from  $4.4 \times 10^{-6}$  to  $1.9 \times 10^{-8}$ .

Postapplication cancer risks for thiophanate-methyl and MBC were not added together in the case of occupational workers. This is mainly because the highest detected MBC residues incurred an MOE of 250, and therefore, postapplication risks from MBC are relatively insignificant compared to those from thiophanate-methyl.

### ***Occupational Risk from MBC Uses***

MBC is a fungicide/preservative formulated as a paste or powder for commercial addition to paint, coatings, plaster, and adhesives; and as a capsule for loading into a tree-injection system. After commercial formulation, MBC-containing paints can be applied by brush, roller, low-pressure hand wand or airless sprayer by professional users.

#### **Occupational Handlers**

EPA has identified two levels of handler exposures:

- Primary handlers -- persons manufacturing end-use products containing MBC (i.e., open-pour addition to coatings, sealants, etc. in the manufacturing process with the paste or powder formulations.
- Secondary handlers -- persons handling paint, coatings, and other products to which MBC has been added.

Since no chemical-specific handler exposure data or studies were submitted, primary and secondary handler exposure estimates were developed using the Pesticide Handler Exposure Database (PHED) Version 1.1 surrogate data. No roller painting, plaster application with a trowel, and sealant

application data are available, but these exposures are assumed to be in the range of exposures estimated for paintbrush and airless sprayer application.

There are no PHED or literature data available for tree injection exposure. The tree injection systems are self-contained products that require no open mixing or direct handling of the product; therefore, the Agency believes that the health risk from tree injection products under normal use is negligible if label use and disposal instructions are followed.

### **Occupational Handlers**

The calculations of short-term and intermediate-term *dermal* exposure indicate that the MOEs are more than 100, and therefore do not exceed the level of concern assuming the use of gloves for mixer/loaders) for four of the five scenarios for which data are available. Only one scenario, mixing/loading/applying ready-to-use paint/stain formulation with a low-pressure hand wand, had a risk that exceeded the level of concern (MOE = 69). This scenario is not of concern when additional PPE is worn.

The calculations of short and intermediate term *inhalation* exposure indicate that the MOEs are more than 100 at **baseline** (no respirator) for all scenarios except adding powdered formulation to paint in the manufacturing process. The calculations for this scenario indicate that the MOE remains less than 100 (MOE = 39) even with the addition of a dust/mist respirator. With engineering controls, the scenario has an MOE greater than 100; however, the practicality of using water-soluble bags for powdered formulation is unknown at this time.

The calculations of total (dermal + inhalation) cancer risk indicate that the estimated risks are between  $1 \times 10^{-5}$  and  $1 \times 10^{-7}$  at baseline for all handler scenarios. All risk estimates were less than  $1 \times 10^{-6}$  with the addition of a dust/mist respirator or engineering controls.

### **Postapplication Workers**

Postapplication occupational exposure to MBC-containing coatings and materials would be primarily via inhalation, as workers would avoid dermal contact until the treated material (paint, sealant, plaster) had dried. Given the uncertainty and lack of information about postapplication exposure to MBC, an accurate quantitative risk estimate is not feasible. However, postapplication exposure to MBC is not considered to be of concern because:

- MBC vapor pressure is low and the amount of active ingredient in the ready-to-use product (maximum 1.5%) is small. The matrix effects of the parent vehicle will further hinder volatilization.
- It is assumed that the handler risk estimates would represent the high-end for possible occupational postapplication exposure. Inhalation MOEs for occupational handlers were  $> 100$  except spraying paint, but this exposure would far exceed any potential postapplication exposure.

- Although the residential exposure would be up to several times as long as occupational exposures, these risk estimates are below the Agency's level of concern.

## **Ecological Risk Assessment**

EPA uses the quotient method to evaluate potential risk to nontarget organisms. Applying this method, risk quotients (RQs) are calculated by dividing the estimated concentrations of a pesticide in the environment by results from ecotoxicity studies in various organisms. A risk concern results when an RQ exceeds a Level of Concern (LOC). An LOC is a value calculated based on the category of nontarget organism and category of concern. EPA further characterizes ecological risk based on any reported aquatic or terrestrial incidents to nontarget organisms in the field (e.g., fish or bird kills).

Because of the rapid degradation of thiophanate-methyl to MBC and the persistence of MBC in soil and water, acute risks to terrestrial and aquatic organisms are assessed based on the assumption that exposure is primarily to thiophanate-methyl and chronic risks to terrestrial and aquatic organisms are assessed based on the assumption that exposure is primarily to MBC.

Effects data indicate that chronic effects are of far greater concern than acute effects, with concentrations at which chronic effects were exhibited being several orders of magnitude lower.

### ***Nontarget Terrestrial Animal Risk***

#### **Risks to Birds**

- The acute LOCs are estimated to be exceeded when thiophanate-methyl is applied to turf, ornamentals, peaches and onions (acute RQs #6.3). Chronic risk quotients, ranging from 0.05 - 283.5, are estimated to exceed the Chronic LOC for most sites, application rates, and frequencies. Consumption of short grass leads to the highest chronic risk estimates for birds.

#### **Risks to Mammals**

- Acute and chronic LOCs for small mammals are estimated to be exceeded when thiophanate-methyl is applied to peaches, turf, ornamentals and onions. Acute RQs are 11.9 or below, and chronic RQs range from 0.38 - 142.3. The estimated risks for smaller mammals tend to be several-fold higher than for larger mammals.

### ***Nontarget Aquatic Animal Risk***

### **Risks to Freshwater Fish and Invertebrates**

- Although the acute high risk LOC was not exceeded, the acute *endangered species* LOC was exceeded based on application to turf and ornamentals (acute RQs #0.5) . Chronic LOCs were exceeded for all crops and locations modeled, with chronic RQs ranging from 7 - 373.

### **Risks to Estuarine/Marine Fish and Invertebrates**

- The acute LOCs were exceeded when thiophanate-methyl is applied to turf, peaches and ornamentals. Chronic LOCs were exceeded for all crops and locations modeled. Acute RQs are 2.46 or below and chronic RQs range from 0.9 to 365.

### ***Nontarget Plant Risk***

- Tier I terrestrial plant toxicity tests indicate low potential for toxicity to 7 of the 10 crop plants tested at up to 1.4 lbs ai per acre; however, additional tests are needed at higher label dosages. Tier II dose response tests for the most sensitive plants, (onion, soybean, and cucumber) must be repeated due to insufficiencies.
- For aquatic plant species, the acute LOCs were exceeded for turf and ornamentals. Methods are not currently available to assess chronic risks to aquatic plants.

## Appendix A: Summary of Residue Values for Thiophanate-methyl

Commodity	Data Source	Translation from Metabolism Study <sup>1</sup>	% Crop Treated		TM (ppm)	MBC + 2-AB <sup>2</sup>
			Avg	Max		
Almond	Field Trial (FT)	sugar beets	10.9	16.4	<0.05	<0.05-0.06(A) <sup>3</sup> <0.05-0.04(C)
Apples	FT	apples	14.5	21.2	<0.05-1.36	<0.05-0.27(A) <0.05-0.27(C)
Apricot	plums FT	apples	10.2	16.7	<0.05-0.31	<0.05-0.22(A) <0.05-0.16(C)
Banana	FT	sugar beets	100	100	<0.20	<0.2-0.11(A) <0.2-0.17(C)
Cherries	FT	apples	3.8	7.2	0.49-14.82	0.2-3.5(A) 0.2-2.5(C)
Cucumber	FT	sugar beets	1.8	2.8	<0.05-0.19	<0.05-0.18(A) <0.05-0.11(C)
Dried Beans	FT	lima bean pod	2.5	8.8	<0.05	<0.05-0.3(A) <0.05-0.2(C)
Green Beans	FT	lima bean pod	3.1	10.1	<0.05-0.7	<0.05-1.4(A) <0.05-1.4(C)
Lima Beans	FT	lima bean pod	3.1	10.1	<0.05-0.09	<0.05-0.11(A) <0.05-0.11(C)
Melons	watermelon FT	sugar beets	2.2	5.5	<0.05-0.27	<0.05-0.25(A) <0.05-0.14(C)
Nectarines	FT	apples	10.2	16.3	0.08-1.92	<0.05-0.34(A) <0.05-0.24(C)
Onions	FT	sugar beets	100	100	<0.05-0.08	<0.05-0.09(A) <0.05-0.06(C)
Pecan	FT	sugar beets	5.9	15.5	<0.05	<0.05-0.06(A) <0.05-0.04(C)
Peaches	FT	apples	26.1	36.6	0.13-2.03	<0.05-1.3(A) <0.05-0.94(C)
Peanuts	FT	sugar beets	1	4.8	<0.05	<0.05-0.06(A) <0.05-0.04(C)
Plums	FT	apples	14.5	21.7	<0.05-0.31	<0.05-0.22(A) <0.05-0.16(C)

Commodity	Data Source	Translation from Metabolism Study <sup>1</sup>	% Crop Treated		TM (ppm)	MBC + 2-AB <sup>2</sup>
			Avg	Max		
Potatoes	FT	sugar beets	100	100	<0.05 <0.05	<0.05-0.06(A) <0.05-0.04(C)
Soybean	FT	lima bean pod	1	1	<0.05-0.09	<0.05-0.4(A) <0.05-0.3(C)
Squash	FT	sugar beets	2.9	4.6	<0.05-0.34	<0.05-0.56(A) <0.05-0.40(C)
Strawberries	FT	sugar beets	21.1	30.7	0.27-5.31	0.16-2.23(A) 0.16-1.58(C)
Sugar Beets	FT	sugar beets	12.1	23	<0.05-0.09	<0.05-0.09(A) <0.05-0.06(C)
Wheat	FT	wheat	1	1	<0.05	<0.05-0.04(A) <0.05-0.04(C)

<sup>1</sup> The ratio from the metabolism study for the specific crops (apple, sugar beet, wheat or lima bean) was used and for dissimilar crops, the most conservative approach (highest ratio from sugar beets-1.45x) was used for acute dietary risk assessment.

<sup>2</sup> The sum of MBC + 2-AB was derived from the ratio of 2-AB with either MBC or TM from the metabolism study.

<sup>3</sup> Range of values used in the acute (A) and chronic (C) assessments.